RESEARCH STATEMENT

Yixin Guo

I focus on two directions in my research. The first direction is on modeling Parkinson's disease (PD) and other movement disorders, deep brain stimulation (DBS) and other brain stimulation toward the study and application using human data. The second is to investigate the spatiotemporal patterns of the neural field model that is related to working memory and other brain functions.

1 Modeling Parkinson's disease and other movement disorders, deep brain stimulations and other brain stimulations.

1.1 Past research

In normal state, the thalamocortial neurons (TC) in the thalamus serve to relay excitatory input from sensorimotor cortex while they are targeted by the inhibitory output from the internal segment of the globus pallidus (GPi) in the basal ganglia. In parkinsonian conditions, a TC neuron fails to respond to excitatory cortical inputs faithfully in a one–to–one fashion, namely, there is one TC voltage spike for each input pulse. The TC cell either fires multiple spikes or no spike at all in response to a single cortical excitatory signal [37, 39]. TC relay failure may be responsible for motor symptoms of Parkinson's disease or other movement disorders. In the past decade, DBS–through a surgically implanted electrode– to the subthalamic nucleus (STN), has become a widely used therapeutic option for the treatment of Parkinson's disease and other neurological disorders. Although the conventional DBS that delivers an ongoing stream of high frequency current pulses to the stimulation target has shown remarkable therapeutic success, neither the mechanisms for the effectiveness of DBS, nor the possible improvement on drawbacks of the conventional DBS are fully addressed. I have done computational studies on investigating the mechanisms underlying the effectiveness of deep brain stimulation (DBS) and improving the conventional DBS to overcome its significant drawbacks. As experimental investigations of DBS mechanism or development of new stimulation protocols are prohibited on humans, or are too costly to be performed on non-human primates, computational study is the necessary first step to advance to clinical application.

1.1.1 Investigating DBS working mechanism

In our previous paper [37], we built a data-driven computational model of a TC neuron to probe why the conventional DBS is therapeutically effective. The model of TC relay neuron is conductance-based Hudgkin-Huxley type with multiple ionic currents. We incorporated GPi spike trains recorded from normal control monkeys, and from parkinsonian monkeys with or without DBS, as the source of inhibitory inputs to our model TC neurons. We tested how biologically observed changes in GPi neuronal activity affect TC signal transmission, both in a single model TC cell and in a heterogeneous population of model TC cells. TC relay fidelity was evaluated using either a periodic or a stochastic train of external excitatory stimuli applied to the same model TC cells that receive the recorded inhibitory synaptic inputs from GPi. Our results show that there is a significant decline in the ability of the TC cells to relay the excitatory stimuli when they are exposed to GPi signals recorded under parkinsonian conditions in the absence of DBS, relative to GPi data recorded from normal monkeys. Moreover, relay effectiveness is restored to non-parkinsonian levels by GPi signals recorded under parkinsonian conditions in the presence of therapeutic DBS. Our computational studies show that GPi firing patterns, produced in parkinsonian conditions without DBS, are, more generally, rhythmic or bursty inhibitory signals with correlations in burst timing across cells. We also found that improvement in TC relay can be achieved by either smearing out the arrival times of correlated, bursty inhibitory GPi signals or replacing the inhibitory GPi inputs from bursty to tonic and high-frequency pattern. As in parkinsonian conditions with therapeutic DBS, TC relay fidelity may be achieved by the latter.

The significant advance in our computational model was to incorporate experimentally recorded GPi firing patterns in the exploration of the mechanism underlying the efficacy of DBS. Even though we adopted a

relatively simple TC cell model, our study lay the groundwork for further exploration in network models that consider the interactions of TC cells and the globus pallidus as well with other brain areas.

1.1.2 Multi-site delayed feedback stimulation (MDFS) using a biophysical model [39]

The conventional DBS has achieved remarkable success in PD patients in relieving motor symptoms. Even thought it has several advantages compared with ablative surgery pallidotomy (destroy part of GPi) or thalamotomy (destroy part of thalamus) in patient's brain, it also has significant drawbacks:

- "Dumb" stimulation [5]: The conventional DBS relies on external force determined by parameters such as type of stimulation (monopolar or bipolar), voltage, frequency (Hz), and pulse width (in ms). Such form of stimulation is considered "dumb" because the external force is not guided by the changes in the brain's electrical activity relevant to the disorder being treated.
- Laborious DBS parameter tuning: It may be a laborious and difficult task to tune the DBS parameters to gain optimal treatment efficacy for a given stage of a disease, especially in patients with movement disorders that would take months to see the therapeutic effect of DBS.
- High energy cost and invasive surgery to replace the battery [4]: It requires surgery of open chest wall to replace the battery of the pulse generator. Energy efficient stimulation is always desirable to prolong battery life and reduce the number of invasive surgeries.

Multi-site Delayed Feedback Stimulation (MDFS) was first suggested as an alternative to the conventional DBS in [41, 42, 43, 72, 79]. The MDFS protocol suggested in these papers has at least two advantages. First, it is noticeably "smarter" in that it is adjusted to brain's own electrical signals. Second, the energy required to administer such stimulation can be maintained at lower level. Although these earlier works contributed toward an excellent idea, the outcomes of MDFS are greatly limited by the choice of model and the focus of study. They all used either non-biophysical phase models or simplified 2-dimensional reduced model that are very limited in describing the neuronal behavior of the basal ganglia. Second, in [42, 41, 43, 72, 79], only self-coupled excitatory population that is representative of the excitatory STN neurons in the basal ganglia were considered. The synchronization mechanism is unfaithful to the anatomy [40] of basal ganglia and the pathology of PD. Further more, the computational work in [42, 41, 43, 72, 79] reported desynchronizing effect on abnormal synchrony of neuron ensembles. Their MDFS neither breaks the bursting pattern nor reduces the higher burst rate which are important characteristics of GPi and STN activity in PD. Most importantly, none of the work in [42, 41, 43, 72, 79] incorporated any criteria to evaluate the downstream neuronal behavior in the thalamus that is relevant to the clinical effectiveness of MDFS.

Rubin and I [39] have recently reported the first work of STN stimulation in the form of MDFS with a biophysical-detailed basal ganglia network model based on Rubin and Terman's model [73]. In MDFS, we calculated the local field potential (LFP) of the stimulation target population and feed back the filtered and delayed LFP signal into the same ensemble through multiple stimulation sites that have different time delays. In [39], both inhibitory population GPe, GPi, and excitatory population STN are included. See Fig. 1 for the connections between populations. There is no self-coupling among the excitatory STN neurons. Therefore the synchronized bursting clusters in STN are not induced by strong excitatory self-coupling such as previous work [41, 42, 43, 72, 79]. Such a setup is consistent with the basal ganglia anatomy that there is not synaptic coupling among excitatory STN neurons [40]. We demonstrated that MDFS applied in STN population not only breaks the pathological synchrony, but also eliminates the bursting patterns presented in STN neurons. The reduction of the average firing rate is a natural result from the burst elimination. We further evaluated the outcome of MDFS by looking at the TC relay fidelity. Our results show that MDFS restores the TC relay ability by desynchronization and burst elimination in a parkinsonian basal-ganglia thalamocortical network. Even though we have some success in this first attempt, the following issues can be further improved:

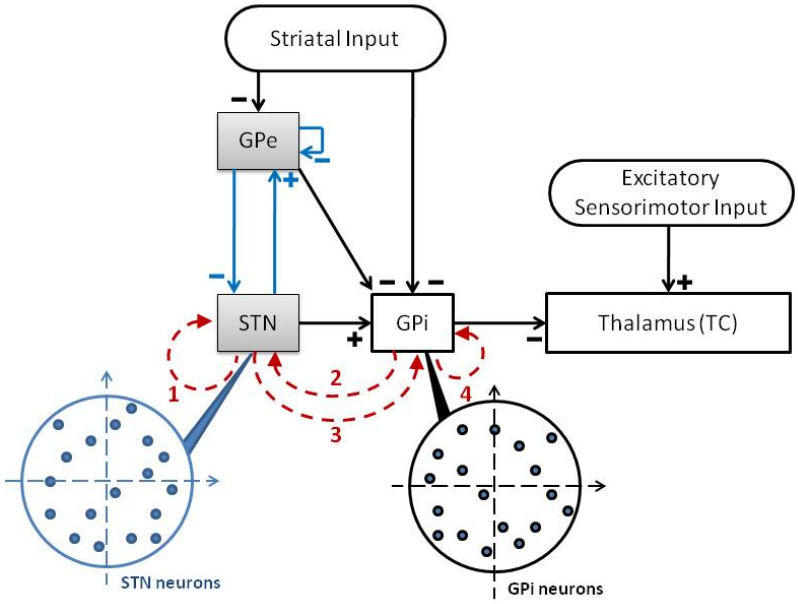

Figure 1: Neuronal structure in the network model. Arrows labelled with a '-' sign represent inhibitory synaptic connections or inputs. Arrows labelled with a '+' sign are excitatory synaptic connections or inputs. All dashed arcs with arrows represent stimulation currents. The tail of the dashed arc is where the stimulation current is gathered. The head of the dashed arrow points to the stimulation target population. The two blowups show the random topological structures of stimulation targets-either STN or GPi. STN and GPe (boxes shaded by light grey) with blue arrows represent the STN–GPe loop.

- Only MDFS administrated on STN was considered in [39]. In clinical practice, both STN and GPi stimulation are commonly practiced on PD patients. GPi as the stimulation target should also be considered in further computational study.
- The network is too small and the spatial structure of the neurons is too rigid to be representative of the real basal ganglia circuit in [39]. There are only tens of neurons in the basal-ganglia network including GPe, STN, and GPi nuclei (16 in each type). Little is known about the geometric structure of the STN neurons. However, the assumption of perfect symmetry in STN neurons and stimulation sites eliminates many possible variations in the administration of MDFS.
- We have shown that MDFS of STN diminishes TC relay error by desynchronization and burst elimination in [39]. However, we did not investigate the extent to which desynchronization and rate reduction resulted in faithful TC relays. Measures in desynchronization and burst reduction should be developed to evaluate the outcome of MDFS.

1.2 Planned study

Based on our previous work, we would like to pursue four studies given in the following four subsections.

1.2.1 Closed-loop DBS

The goal in this study is to develop energy efficient and "smarter" closed-loop DBS protocols, guided by changes in neuronal activities specific to disorders being treated. We will first build a large-scale biological-faithful computational network consisting of hundreds of neurons in each nucleus, and a wide range of geometric spatial structure in the stimulation target population. We will then develop and test

several novel closed-loop DBS protocols that applies MDFS stimulation on various targets in the network based on the feedback signals collected within basal ganglia. We aim to find a plausible MDFS administration with appropriate choices of multiple stimulation sites and parameters. We will develop new quantitative measures for the outcome of MDFS, in addition to TC error index in the prior work, to quantify desynchronization and burst rate in the stimulated population.

1.2.2 Chimera state

A mathematical chimera is a state in which an array of oscillators splits into two co-existing sub-populations: one coherent and synchronized with unique frequency, and the other incoherent and desynchronized with distributed frequency [1, 2, 44, 46, 47, 49, 50, 55, 58, 59, 60, 76, 77]. Such a state was first noticed by Kuramoto and his colleagues [45, 46] while simulating the complex Ginzburg-Landau equation with non-local coupling.

Computational models of uncoupled GPi neurons in the basal ganglia exhibit wide range of behavior including synchronization, desynchronization, and clustering [39, 73, 78]. The coexistence of synchrony and asynchrony, which is the chimera state, has not been shown. We will study the emergence of chimera sates in GPi neurons in the basal ganglia.

We focus on the GPi ensemble for the following reasons. First, GPi is the major output from basal ganglia directly connected to TC cells in thalamus. Abnormal synchrony and firing patterns of GPi neurons compromise TC relay to motor cortex which may be responsible for the motor symptoms in PD and other movement disorders [31, 32, 33]. If we find ways to break the synchrony and/or reduce burst rate in GPi neurons, we can restore TC relay ability. Second, finding the chimera state in GPi populations in a parkinsonian network could be a significant breakthrough in developing systematic methods for synchrony breaking and burst rate reduction, as chimera states are considered as a natural transition between synchrony and asynchrony [56, 58]. The important factors in the emergency of chimera states may help to develop mild and effective DBS in movement disorders characterized by abnormal neuronal firing patterns and pathological synchrony.

We hypothesize that the initial states of the GPi oscillators are the key to breaking the full synchrony, to eliminating the uniform bursting pattern, and, consequently, to finding the chiemra states in the ensemble. As Motter [56] and Omel'chenko et. al. [58] suggested, in an ensemble of coupled oscillators, synchronization and desynchronization depend on the *intrinsic properties*, the *coupling structure* of the oscillators, and the *initial state* of each oscillator. The synchrony in GPi population is neither due to the coupling between GPi oscillators (there is no synaptic coupling among GPi neurons) nor due to their intrinsic properties. The GPi synchrony is entrained by the upstream structure–the STN-GPe loop in which both STN and GPe are in synchronous bursting clusters. The main focus of our investigation will be on initial states which refer to the initial conditions of five nonlinear differential equations for GPi oscillators.

Our goal is to pin down the initial conditions of GPi neurons that can break the full synchrony by settling GPi oscillators into different stable limit cycles while maintaining the parkinsonian STN-GPe common input to GPi. We will reduce the 5-D GPi oscillator to a 2-D map that can assist us in estimating such initial conditions. The fixed points of the 2-D map correspond to periodic solutions of the original 5-D system. Using fixed points of the 2-D map, we will identify stable limit cycles of different periods, stable limit cycles with various number spikes in each cycle, and stable subthreshold oscillations. These different scenarios correspond to periodic patterns when a GPi neuron fires a single spike, or double spikes (triples or even more spikes), or a subthreshold spike during each period. We will use the fixed points of the 2-D map to estimate the initial conditions of the original 5-D system in which we will be able to find all different types of coexisting periodic patterns.

We propose a two-step approach to find chimera states in the synchronous GPi ensemble. We will split the whole ensemble with N neurons into two subgroups with P and Q neurons each, where $P + Q = N$. First, we break the synchrony and eliminate uniform bursts in one subgroup, say P, by making neurons settle in different limit cycles. Second, for a subpopulation of P that are synchronously settled in the same limit cycle,

we will apply the localized desynchronization method by Danzl et. al. [16] which will effectively desynchronize this subpopulation of P. We may repeatedly apply the second step to all synchronous subpopulations in P. Eventually, neurons in group P will become asynchronous with various periodic firing patterns. We may further make a connection with the study on the relation between TC relay error index EI, synchrony level R, and burst rate r_b. We can choose the P number to reach the level of R and r_b that is necessary for TC relay error lower than that in parkinsonian state. As we vary the P number, we may be able to provide theoretical explanations of the transition between normal and parkinsonian states through changes in synchrony and burst rate.

Corresponding to the two steps in finding chimera states, we may suggest a new DBS protocol that can administer two type of stimulation signals. One signal is a shock wave to reset initial states of a subgroup of GPi neurons into different stable states. The second signal is a mild phase-correcting impulses with minimal energy through charge-balanced optimization [16].

The planned study given in section 1.2.1 and 1.2.2 will be funded by NSF, DMS from September 2012 to August 2015. I will recruit one or two Ph. D. students partially funded by this grant to work on this two projects.

1.2.3 Study TC relay using human patient data

One limitation of our previous data-driven TC relay model [37] is the lack of human data. Supported by the Antelo Devereux award for Young Faculty at Drexel University, I have formed collaboration with medical doctor Robert Worth and Leonid Rubchinsky's research group at the Indiana University Purdue University Indianapolis (IUPUI). My collaborator provided me human GPi data from parkinson's and dystonic patients. Our goal is to compare the relay responses of TC neurons under GPi inhibition from both dystonia and Parkinson's patients.

Dystonia is a widespread neurological disorder characterized by sustained muscle contractions, involuntary repetitive movements and abnormal posture. Although the exact pathophysiological mechanism remains unknown, dystonia is also marked by the presence of oscillatory activity that may affect the efficiency of TC relay and thus contribute to symptoms in dystonic condition.

We use a computational model of thalamo-cortical relay, modulated by real data recorded in GPi of parkinsonian and dystonic patients, to explore the differences and similarities between parkinsonian and dystonic thalamocortical relay. The use of the real pallidal recordings in the computational model may be a substantial advantage. The real data will allow us to capture the response of thalamocortical relay not only to bursting in a specified frequency range, but to real pallidal activity with its specific complex temporal structure.

1.2.4 Map reduction of the TC relay model

The goal of this study is to find all the dynamical states of TC relay responses to bursting GPi inhibition of various burst durations and inter-burst intervals. This is a joint work with postdoc Dennis Guang Yang. We will study the 3D conductance-based model of the single thalamocortical (TC) neuron given in [37] in response to sensorimotor signals. In particular, we focus on the entrainment of the system to periodic signals that alternate between 'on' and 'off' states lasting for time T_{on} and T_{off}, respectively. By exploiting invariant sets of the system and their associated invariant fiber bundles that foliate the phase space, we reduce the 3D Poincaré map to the composition of two 2D maps and also simplify the two components of the 2D maps to a uniform shift and a uniform decay. Then based on these 2D maps, we analyze the bifurcations of the entrained limit cycles as the parameters T_{on} and T_{off} vary.

2 Spatiotemporal patterns of the neural field model

The second direction of my research concerns spatiotemporal patterns of the following neural field model, also called the firing rate model, for neural networks with non-saturating gain and various network architectures.

$$\frac{\partial u(x,t)}{\partial t} = -u(x,t) + \int_{-\infty}^{\infty} w(x-y) f(u(y,t)) dy, \tag{1}$$

where $u(x,t)$ is the synaptic input to neurons located at position $x \in (-\infty, \infty)$ at time $t \geq 0$, and it represents the level of excitation or amount of input to a neural element. The coupling function $w(x)$ determines the connections between neurons.

Our primary goal is to investigate the existence and stability of standing and traveling patterns of (1). The long term goal is to explore thoroughly the dynamics of the firing rate model, probe transition between standing and traveling patterns, and map out the bifurcations of spatiotemporal patterns.

2.1 Previous results

2.1.1 Standing pulses

- Existence and stability of single-bump standing pulses

Experiments on delayed response tasks find that a specific set of neurons in the prefrontal cortex become activated by a transient visual cue. They fire at a rate above their spontaneous levels while the memory of cue location is being held in mind for several seconds and then return to the baseline levels after the memory is no longer needed [7, 8, 12, 25, 26, 27, 28, 29, 69, 71]. How are these neurons able to persist in active state during the working memory period without external stimulus? Previous work probed the question using one-population firing rate model with saturating gain functions, which implies that neurons start to fire when their inputs exceed threshold and saturate to their maximum rate quickly [3, 15, 64, 63, 66, 84]. However, experimental evidence has shown that persistently active neurons fire at rates far below their saturated maximum and the firing rate increases linearly with input [9, 10, 11, 12, 13, 26, 30, 53, 54, 61, 70, 71, 81, 82]. To resolve the conflict between the analytical study and experimental observation, we have fully analyzed the existence and stability of 1–bump standing pulses of the firing rate model (1) with non-saturating piecewise linear gain (2) and lateral inhibition connectivity (3) [34, 35, 36].

$$f(u) = (\alpha(u - u_T) + 1)\Theta(u - h), \tag{2}$$

where $\Theta(u-h)$ is the Heaviside function, α is the gain, and u_T is the threshold.

$$w(x) = Ae^{-a|x|} - e^{-|x|}, \text{where } a,\ A > 1. \tag{3}$$

where a, $A > 1$.

A standing pulse solution, the "so-called" N-bump ($N \geq 1$) solution $u(x)$, of (1) satisfies the following equilibrium equation of the dynamical system (1).

$$u(x) = \int_{-\infty}^{\infty} w(x-y) f(u(y)) dy \quad \text{for all } x \in \mathbf{R}, \tag{4}$$

In [35], we showed the existence of 1–bump standing pulse of (4). We applied Fourier transform to decompose the convolution that appears on the equilibrium equation (4) and to obtain a fourth order ordinary differential equation (ODE) including singular terms from the discontinuity in the gain function. A one-bump solution of (4) corresponds to a homoclinic orbit of the boundary value problem of the ODE. From the fourth order ODE, we constructed different 1–bump solutions. For a fixed gain α and synaptic coupling, we found two one–bump solutions, a "large" one that is tall and wide and a "small" one that is short and narrow. In [36], we proved that the large 1–bump standing pulse is stable, and the small one is unstable. We also found that the firing rate network has stable 1–bump standing pulses when inhibition dominates excitation and the gain is not too large.

- Multi-bump standing pulses

Multi-bump solutions ($N \geq 2$) of (4) have been studied mainly using numerical techniques [15, 21, 48]. The common approach of these previous works is to transfer (4) to an equivalent ODE and use numerical continuation to discover a rich family of N-bump solutions and their bifurcations. Although, their ODEs may be different due to their choices of coupling and gain functions. As Laing et al pointed out in [48], rigorous proof of multi-bump solutions of the equivalent ODE is already a challenging problem. A rigorous proof of the existence of multi-bump solution of the integral equation (4) with nonspecific coupling and gain functions is even a more challenging task.

More recently, Faugeras et. al. have studied the local and global structure of stationary solutions using a very general coupling function with mild hypotheses as square integrable and a smooth sigmoidal gain that is infinitely differentiable [19, 20, 80]. While their functional analysis approach did open up a new direction to study the neural field model, they deviated from the classic Amari model (4) by relaxing the infinite domain of the neural field model to a connected and compact domain that is a subset of $\mathbf{R}$ [20, 80]. Their methods and results are not applicable to (4) with non-compact infinite domain.

The objective of the manuscript [83] is to establish the existence of stationary multi-bump solutions of (4) using even, bounded and Lipschitz continuous coupling functions and a general class of gain functions. Our strategy involves building a nonlinear map based on Newton's method, proving this map is a contraction in an appropriate neighborhood centered at a special function which we name as reference solution, and showing that a fixed point of the nonlinear map is a stationary multi-bump solution of (4).

Our work advances previous results on multi-bump solutions [15, 21, 48] in the following aspects. First, we prove the existence of multi-bump solutions of (4) with much more general kernel and gain functions. As all previous multi-bump existence of (4) were shown numerically for specific kernels and gain functions. Secondly, we make a connection between our rigorous proof and a multi-bump numerically calculated [48], named as a reference solution in our proof. We use a reference solution as the center of the neighborhood where the contraction converges to a unique fixed point that is a multi-bump solution of (4) with general coupling and gain functions.

2.1.2 Traveling fronts in a lateral inhibition network

Firing rate model (1) has rich dynamics. When the stability of standing pulse is lost, it is expected to see a transition from standing patterns to traveling waves, such as traveling fronts or traveling pulses. Neuronal waves have been observed in vitro experiments and in sensory processing such as visual [6, 67, 68, 75], somatosensory [22, 57, 62] and olfactory [23, 24, 51, 52]. Neurological disorders such as epilepsy are also characterized by propagating activity across the cortex [14].

Inspired by Ermentrout and McLeod, and Zhang's previous study on traveling fronts [18, 84], We have investigated the existence and stability of traveling fronts of the firing rate model (1). We extend their work in two aspects. First we show the existence of non-monotonic traveling front solutions of (1) with 'Mexican Hat' type of lateral inhibition coupling and non-saturating piecewise linear gain as Ermentrout and McLeod [18] and Zhang [84] considered only excitatory coupling function. Second, we extend Zhang's approach using the integral Evans function to the lateral inhibition networks with the Heaviside gain. We show that there is no eigenvalue with positive real part for traveling fronts existing in the parameter ranges we consider. Since Zhang's integral Evans function approach cannot be extended to stability analysis of traveling fronts with non-zero gain, we further investigate numerically the stability of lateral inhibition network with non-zero gain. Results in this study will appear in the SIAM journal on Applied Dynamical Systems [38].

2.2 Future plan

I planned to do the following series of studies on the firing rate model of neural networks.

2.2.1 Stability of traveling fronts of non-zero gain

We did not analyze the stability of traveling front solution of (1) with non-zero gain in [38]. Since we can no longer apply Zhang's integral Evans function approach, we will develop a different analytical approach to handle the linear stability analysis for piecewise linear gain function with non-zero gain. It is expected that both analytic derivation and numerical computation in finding the essential spectrum and point spectrum are significantly more complicated compared with the integral Evans function approach [84].

2.2.2 Asymmetric multi-bump standing pulses

Dennis Guang Yang and I have developed a method of geometric construction of N–bump standing pulses ($N \geq 3$) of (4) with the 'Mexican Hat' coupling (3) and piecewise linear gain (2) using the same 4–dim ODE system given in [35]. We are interested in different method of constructing multi-bump standing pulses. We could use the same approach as in [35] to construct N-bump solution with $N \geq 3$. However, the process will be tedious and it is more difficult to solve the system of algebraic equations to construct $N-bump$, especially for asymmetric standing pulses because the equations number goes up quickly as the number of bumps increases. Moreover, it is difficult to show the coexistence of N-bump solutions (N=1, 2, 3,...).

In the geometric construction, we build a map F going from the local unstable manifold of the zero equilibrium state to its stable manifold (shown in Figure 2).

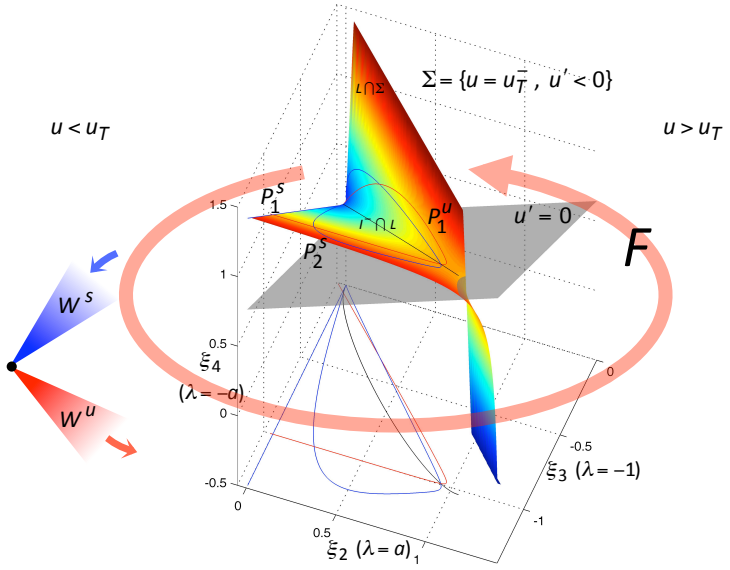

Figure 2: Construction of map F.

The 3–D interface Σ in Figure 2 is where $u = u_T$. The colored surface in Figure 2 is the intersection of Σ and L that is the level set of conserved energy. Now the global stable and unstable manifolds of zero fixed point, W_s and W_u, intersect transversally in $\Sigma \cup L$. Then we can pin down the point where W_s and W_u meet each other. Our preliminary study shows the this geometric construction not only gives us all the symmetric and asymmetric $N-bump$ standing pulses and also provides a clear view on how they coexist. Interestingly, there is a horseshoe structure when the region R is stretched and folded under the map F and its inverse F^{-1}, where R is the enclosed region by the projection of P_1^u, which is the first intersection W_u with Σ, and P_1^s, the first intersection of W_s with Σ, onto the 2–D plan in the interface Σ. See Figure 3 for an example of 3-bump pulses.

Based on our preliminary investigation, we would like to do a thorough study and finish all the proofs of the geometric construction and the horseshoe structure.

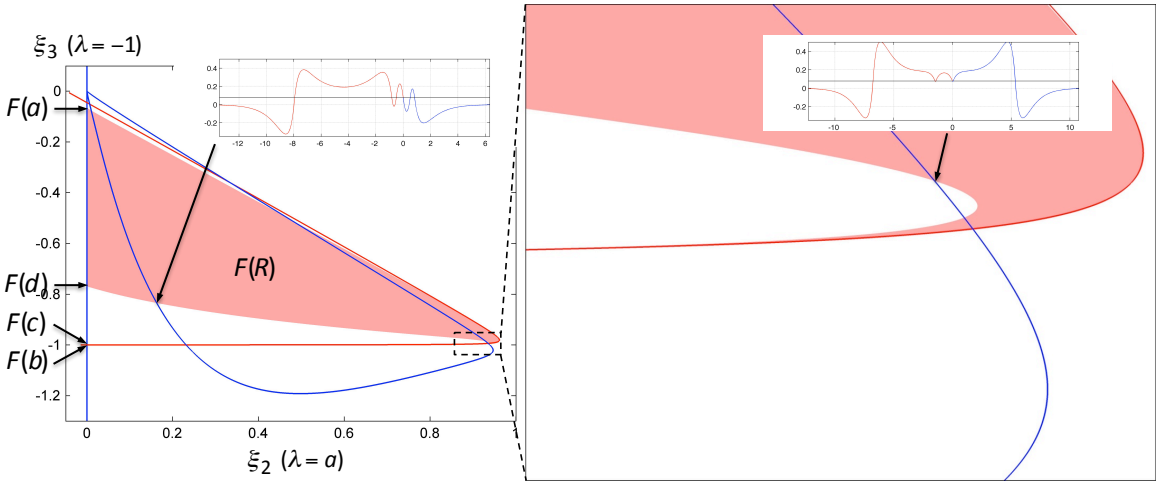

Figure 3: The coexistence of symmetric and asymmetric 3–bump standing pulses occurs at the intersection of the blue curve and the red curve. Total there are 2^3 number of symmetric and asymmetric 3–bump standing pulses. 4 are symmetric 3–bump pulses and the other 4 are asymmetric ones.

2.2.3 Traveling Pulses in an Excitatory Network with Negative Feedback

Neurons in propagating pulses are recruited because of the excitatory interactions. Nevertheless, excited state of cells in the brain does not remain indefinitely. Inhibition can disrupt any type of wave propagation. In the absence of synaptic inhibition, the intrinsic ionic processes within the cell such as adaptation can also repolarize the network. Experimental evidence has proved that inhibition is necessary for the initiation and termination of traveling pulses [66]. Moreover, inhomogeneities in velocity in different cortical areas were discovered experimentally. At recruitment cycle, a group of inhibitory neurons is excited, and in turn, it inhibits a new group of excitatory cells. After these excitatory neurons rebound from hyperpolarization, they recruit a new group of cells. To fully understand the circuitry mechanism for spatiotemporal traveling pulses, we must include inhibition into the network.

Amari considered a neural field consisting of excitatory and inhibitory cells [3]. Besides recurrent connection within the excitatory group, the excitatory neuron at location x only excites the inhibitory neurons at place x. Inhibitory neurons merely inhibit the excitatory ones. Amari had the following field equation

$$\tau u_t(x,t) = -u(x,t) + \int w_{ee}(x-y)H(u(y,t))dy - \int w_{ie}(x-y)H(v(y,t))dy + h_1 \quad (5)$$

$$\tau v_t(x,t) = -v(x,t) + w_{ei}(x)H(u(x,t)) + h_2 \quad (6)$$

with $u(x,t)$ and $v(x,t)$ being the excitatory and inhibitory input, respectively, h_1 is the threshold for excitation, the Heaviside function $H(u(x,t)) = 1$ if $u > h_1$, otherwise, $H(u(x,t)) = 0$, the threshold for the inhibitory firing rate $H(v(x,t))$ is h_2. Amari used same time constants for both inhibition and excitation. It has been argued that in two-population continuous model, a difference in time constant is necessary to get traveling pulses [17, 64].

One can generalize Amari's system to a two-population model with excitatory firing rate function $f_e(u)$ and inhibitory gain function $f_i(u)$

$$u_t(x,t) = -u(x,t) + \int w_{ee}(x-y)f_e(u(y,t))dy - \int w_{ie}(x-y)f_i(v(y,t))dy \quad (7)$$

$$v_t(x,y) = \epsilon[-\beta v(x,t) + w_{ei}(x)f_e(u(y,t))] \quad (8)$$

where β is the decay of negative feedback, and ϵ results from rescaling the inhibitory and excitatory time constants.

Pinto studied a simpler system in which both the inhibition and the effect of excitation on inhibitory neurons are linear [64]. He also assumed that the decay of negative feedback is weak (i.e. $\beta = 0$) and used the Heaviside function for excitatory firing rate. Then system (7) and (8) become

$$u_t(x,t) = -u(x,t) + \int w_{ee}(x-y)H(u(y,t))dy - v(y,t) \tag{9}$$

$$v_t(x,t) = \epsilon u(x,t) \tag{10}$$

This model can be viewed as a one-population network of excitation with negative feedback that could be from synaptic depression, spike frequency adaptation or other intrinsic slow process.

Both Amari and Pinto sought traveling pulse solutions $u(x-ct)$ with velocity c as defined in the previous section. Such solutions represent propagating regions of excitation where the excitatory population is above the threshold u_h on a finite spatial interval $(0, a)$. Amari showed that there is a traveling pulse solution [3]. It was not clear whether such a traveling pulse is unique. Pinto showed that there are two traveling pulses, one is with fast speed and wider pulse, the other is slow and narrow. Pinto arrived the conclusion that the fast pulse is stable and the slow one is unstable by numerical simulations. Later, Zhang rigorously proved the linear stability for the fast traveling pulse [85]. In [65], Pinto et al. studied system (9) and (10) with one more term $-\beta v(x,t)$ adding to (10). They demonstrated the existence of two traveling pulse solution when neurons have a single stable state. They also showed the existence of a stationary pulse solutions and a single traveling pulse solution. They constructed the Evens function to probe the stability of the standing and traveling pulses. All this work was based on Heaviside gain function. Sandstede later revisited the construction of Evans function of the same model [74]. He rigorously showed the reduction of Evans function constructed in [65]. His proof generalized the derivation of Evans function for the class of Heaviside gain function.

We will examine traveling pulses in a more general system with biological realistic gain function $f_e = (\alpha(u-u_h)+1)H(u-u_h)$.

For mathematical simplification, we will assume that the inhibitory to excitatory connection in (7) is independent of the distance between neurons and the firing rate for inhibition is purely linear. One can simplify (8) by assuming $w_{ei}(x)$ is constant. Without loss of generality, one can set $w_{ei} = 1$. We will obtain the following system

$$u_t(x,t) = -u(x,t) + \int w_{ee}(x-y)f_e(u(y,t))dy - v(x,t) \tag{11}$$

$$v_t(x,y) = \epsilon[v(x,t) + \beta f_e(u(y,t))] \tag{12}$$

One could probe whether system (11) and (12) has a traveling pulse using singular perturbation [17, 64]. However, such a construction will only identify one solution if there are any. When there are more than one traveling pulses, such as in Pinto's study, fast stable one and slow unstable one, singular perturbation construction will certainly miss one. One may think it is harmless to miss the unstable traveling pulse, but it is as crucial to identify any unstable solutions to understand the dynamics of the system. Therefore, we will study the system by transforming the integro-differential equations (11) and (12) into a system of high order ordinary differential equations. After rigorously showing that solutions of system (11) and (12) solve the derived ODE system and vice versa, we can analyze the existence and stability of traveling patterns of the ODE system using theories in ODE and dynamical systems.

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- Yixin Guo. Existence and stability of traveling fronts in a lateral inhibition neural network. SIAM J. on Applied Dynamical Systems, to appear, 2012.

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- Yixin Guo and Jonathan E. Rubin. Multi-site stimulation of subthalamic nucleus diminishes thalamocortical relay errors in a biophysical network model. Neural Networks, 24(6):602{16}, 2011.

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- Y. Guo and C.C. Chow. Existence and stability of standing pulses in neural networks: II. stability. SIAM J. on Applied Dynamical Systems, 4 (2):217-248, 2005.

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